EXHIBIT 55

American Thoracic Society Documents

Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos

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Asbestos is a general term for a heterogeneous group of hydrated magnesium silicate minerals that have in common a tendency to separate into fibers (1). These fibers, inhaled and displaced by various means to lung tissue, can cause a spectrum of diseases including cancer and disorders related to inflammation and fibrosis. Asbestos has been the largest single cause of occupational cancer in the United States and a significant cause of disease and disability from nonmalignant disease. To this demonstrable burden of asbestos-related disease is added the burden of public concern and fear regarding risk after minimal exposure.

This statement presents guidance for the diagnosis of nonmalignant asbestos-related disease. Nonmalignant asbestos-related disease refers to the following conditions: asbestosis, pleural thickening or asbestos-related pleural fibrosis (plaques or diffuse fibrosis), "benign" (nonmalignant) pleural effusion, and airflow obstruction. This document is intended to assist the clinician in making a diagnosis that will be the basis for individual management of the patient. It therefore provides overarching criteria for the diagnosis, specific guidelines for satisfying these criteria, and descriptions of the clinical implications of the diagnosis, including the basic management plan that should be triggered by the diagnosis. It is understood that disease may be present at a subclinical level and may not be sufficiently advanced to be apparent on histology, imaging, or functional studies.

One of the most important implications of the diagnosis of nonmalignant asbestos-related disease is that there is a close correlation between the presence of nonmalignant disease and the risk of malignancy, which may arise from exposure levels required to produce nonmalignant disease or mechanisms shared with premalignant processes that lead to cancer. The major malignancies associated with asbestos are cancer of the lung (with a complex relationship to cigarette smoking) and mesothelioma (pleural or peritoneal), with excess risk also reported for other sites. There is a strong statistical association between asbestos-related disease and malignancy, but the majority of patients with nonmalignant asbestos-related disease do not develop cancer. On the other hand, the risk of cancer may be elevated in a person exposed to asbestos without obvious signs of nonmalignant asbestos-related disease. However, a diagnosis of nonmalignant asbestos-related disease does imply a lifelong elevated risk for asbestos-related cancer.

DIAGNOSTIC CRITERIA AND GUIDELINES FOR DOCUMENTING THEM

People with past exposure to asbestos consult physicians for many relevant reasons: to be screened for asbestos-related disease, for evaluation of specific symptoms that may relate to past asbestos exposure (known or unsuspected), for treatment and advice, and for evaluation of impairment. In 1986, the American Thoracic Society convened a group of experts to review the literature and to present an authoritative consensus view of the current state of knowledge with respect to diagnosis of nonmalignant disease related to asbestos (2). In 2001, a new group was convened to review and to update the 1986 criteria. This statement constitutes that committee's report, completed in 2004.

The criteria formulated in this statement are intended for the diagnosis of nonmalignant asbestos-related disease in an individual in a clinical setting for the purpose of managing that person's current condition and future health. These general criteria are slightly modified from those presented in 1986 (Table 1) (2):

- Evidence of structural pathology consistent with asbestos-related disease as documented by imaging or histology
- Evidence of causation by asbestos as documented by the occupational and environmental history, markers of exposure (usually pleural plaques), recovery of asbestos bodies, or other means
- Exclusion of alternative plausible causes for the findings

The rest of this statement is largely devoted to presenting clinical guidelines required to document that each of these criteria is met. Demonstration of functional impairment is not required for the diagnosis of a nonmalignant asbestos-related disease, but where present should be documented as part of the complete evaluation. Evaluation of impairment has been exten-

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been coated with an iron-rich, proteinaceous concretion (Figures 1 and 2). Amphibole asbestos forms the majority of asbestos bodies and is more persistent in lung tissue than chrysotile (25). Asbestos bodies are larger than asbestos fibers and can be identified and quantified by light microscopy. An iron stain is helpful to identify fibrous bodies coated by iron (hence the general name "ferruginous bodies"). Ferruginous bodies generally form on fibers at least 10 μm in length, and more than 90% of all coated fibers have asbestos cores. Demonstration of an elevated body burden of asbestos confirms past exposure (19). Levels of at least one or two asbestos bodies per field of a tissue section on a slide under light microscopy are consistent with occupational exposure (19, 22, 24).

Transbronchial biopsy. Transbronchial lung biopsies are usually too small to analyze for asbestos bodies. Bronchoalveolar lavage recovers more material and therefore provides a better indicator of tissue burden. Some experienced clinicians have found that identification of six or more bodies in bleach-digested samples from at least two biopsies is characteristic of patients with occupational exposure (26). However, the absence of observable asbestos bodies is not reliable in excluding significant exposure in transbronchial biopsy tissue (20).

These indicators of fiber burden are sufficient but not necessary to identify occupational exposure and to diagnose asbestos-related disease. Beyond clinical research, the method has applications in litigation and exposure assessment for epidemiology.

Bronchoalveolar lavage. Asbestos bodies and fibers can be identified and quantified in BAL specimens, as in Figure 2 (22). There is considerable variation among laboratories in these tests (18, 19, 22, 23). The count of asbestos bodies in BAL fluid appears to correlate with the presence or degree of fibrosis in some studies but not others (24, 27, 28).

BAL in patients with asbestosis has demonstrated an alveolar macrophage alveolitis associated with a modest increase in neutrophils (12, 13). This neutrophilia correlates with the finding of crackles (rales) on physical examination and disturbances in oxygenation (12, 27) and is apt to be more pronounced in patients with advanced disease (13). Clinically apparent asbestosis occurs only after a significant latent period. However, studies using BAL, computed tomography (CT) scanning, and gallium-67 scanning have demonstrated that inflammatory events occur well before the onset of clinical disease. Thus, it is likely that the initial exposure induces inflammation and injury that persist through the latent or subclinical phase and later develop into the clinical disease, which is typically diagnosed by chest imaging (13).

CLINICAL EVALUATION AND INDICATORS

The clinical evaluation of nonmalignant asbestos-related disease should consider subjective symptoms as well as objective findings on physical examination, pulmonary function tests, and chest radiographic studies. In the large majority of patients, the diagnosis of nonmalignant asbestos-related lung disease is based on the clinical findings discussed below, in the context of an appropriate history of exposure to asbestos and a documented latency period sufficient to place an individual at risk.

Symptoms

The insidious onset of dyspnea is the most common respiratory symptom associated with asbestosis, typically beginning with dyspnea on exertion. A nonproductive cough is commonly present. The presence of wheeze or dyspnea (27), as reported on the ATS-DLD-78A respiratory questionnaire (5), is strongly associated with diminished ventilatory capacity in cross-sectional studies of asbestos-exposed workers, with an 11 to 17% reduction in ventilatory capacity (27, 29). A 2–8% reduction in ventilatory capacity has been observed for cough, phlegm, and symptoms of chronic bronchitis among asbestos-exposed workers (29). Development or progression of respiratory symptoms has been associated with accelerated loss of ventilatory capacity in a longitudinal investigation of asbestos-exposed workers, with an excess 28-ml/year decline in FEV_1 associated with development of dyspnea, and 67-ml/year excess decline in FVC associated with newly developed wheezing, relative to asymptomatic individuals (30).

In a study of 64 patients, diffuse pleural thickening or fibrothorax was associated with dyspnea on exertion, usually mild, in 95%, chest pain in more than half, and restrictive defect in one-third. The chest pain was intermittent in most but constant in 9% (31). Rapidly progressive or severe chest pain should raise clinical suspicion of either malignancy or a nonmalignant pleuritis.

Subjective symptoms are not easily interpreted in the absence of objective findings but provide important ancillary information. The persistence or new onset of respiratory symptoms is correlated with accelerated loss of lung function in asbestos-exposed workers and therefore may predict future risk (30).

Occupational and Environmental History

It is essential to take a comprehensive occupational and environmental history when asbestos-related disease is suspected (32). The occupational history should emphasize occupational and environmental opportunities for exposure that occurred about 15 years and more before presentation.

The diagnosis of asbestosis is ideally based on an accurate exposure history, obtained whenever possible directly from the patient, that defines the duration, intensity, time of onset, and setting of exposure experienced by the patient. Patients may forget short periods of employment, during which intense exposure is possible, or employment early in their lives. In such cases the characteristic radiographic signs of asbestos exposure may be enough to document exposure.

The occupational title is not enough, as the names of many occupations and trades are uninformative, such as "millwright" or "fireman" (a misleading title that sometimes refers to furnace workers and stokers) or "mixer." Representative occupational exposures include, but are not limited to, manufacture of asbestos products, asbestos mining and milling, construction trades (including insulators, sheet metal workers, electricians, plumbers, pipefitters, and carpenters), power plant workers, boilermakers, and shipyard workers.

Asbestosis is commonly associated with prolonged exposure, usually over 10 to 20 years. However, short, intense exposures to asbestos, lasting from several months to 1 year or more, can be sufficient to cause asbestosis. For example, shipyard workers who applied or removed insulation in confined spaces have developed asbestosis after brief periods of heavy exposure. Insulation workers have had similarly intense exposures during their apprenticeship when they unloaded asbestos-containing sacks into troughs for mixing asbestos cement. Such occupational exposures are now rare but were common in the United States from the years after World War II until the 1970s. Adequate industrial hygiene controls were absent or not widely applied. Protective regulations were inadequate and only partially enforced during much of that period.

Workers whose own jobs may not require handling asbestos may still be "bystanders" who worked in close proximity to other users, especially in the construction trades, where workers have experienced exposure from insulation being installed around them. Among sheet metal workers, for example, the prevalence of asbestos-related changes on chest film was 31% (19% pleural only, 7% parenchymal only, and 6% both). Among those who had been in the trade for 40 or more years, 41.5% had radio-

sufficient to differentiate asbestosis from other forms of interstitial fibrosis. The chance of finding one asbestos body from background exposure alone has been shown to be about 1 per 1,000 (79). Conversely, the presence of interstitial fibrosis in the absence of asbestos bodies is most likely not asbestosis, although rare cases of pulmonary fibrosis with large numbers of uncoated asbestos fibers have been described (80–82). Idiopathic pulmonary fibrosis (IPF in clinical terms or usual interstitial pneumonitis in terms of pathology) has an acinar pattern of fibrosis different from that of asbestosis and is not associated with asbestos bodies in tissue sections. On occasion, asbestosis is seen in conjunction with an unrelated interstitial lung disease (such as sarcoidosis) or in association with another pneumoconiosis, for example, silicosis. In the absence of fibrosis, asbestos bodies are an indication of exposure, not disease.

Asbestosis resembles a variety of other diffuse interstitial inflammatory and fibrotic processes in the lung and must be distinguished from other pneumoconioses, IPF, hypersensitivity pneumonitis, sarcoidosis, and other diseases of this class. The clinical features of asbestosis, although characteristic, are not individually unique or pathognomonic, but the characteristic signs of the disease are highly suggestive when they occur together. The presence of pleural plaques provides useful corollary evidence that the parenchymal process is asbestos related.

Diagnostic uncertainty is most likely in certain groups of patients. Patients may have a heavy cigarette-smoking history and concurrent emphysema (which also reduces the diffusing capacity). In such cases, one expects a history of asbestos exposure commensurate with the degree of disease. On occasion, a patient with another interstitial lung disease, such as IPF, will have a history of asbestos exposure. Rapid progression, with a visible, year-to-year increase in symptoms, progression of radiographic findings, and loss of pulmonary function in the absence of intense asbestos exposure, suggests the diagnosis of IPF rather than asbestosis.

Patients may be exposed at various times in their working life to more than one dust, such as silica and asbestos, or to mixed exposures, such as dusts in combination with fumes and vapors in welding (83). These patients may have combined disease or the effects of one dust or other exposure may dominate. For example, predominantly upper lobe rounded opacities, hilar node enlargement, and progressive massive fibrosis are not features of asbestosis and if present suggest other causes for the lung disease than asbestos, such as silicosis.

On occasion, isolated fibrotic lesions associated with asbestos resemble solitary pulmonary nodules. These are sometimes called "asbestomas" and usually occur against a background of irregular opacities; they rarely appear in isolation. They normally require biopsy because they are not distinguishable from lung malignancies otherwise (84).

Nonmalignant Pleural Abnormalities Associated with Asbestos

Pleural abnormalities associated with asbestos exposure are the result of collagen deposition resulting in subpleural thickening, which may subsequently calcify, and which in the visceral pleura may be associated with parenchymal fibrosis in adjacent subpleural alveoli (Figures 10 and 11). Pleural thickening, as a marker of asbestos exposure, has continued to be a prominent feature of exposure to asbestos while other outcomes, such as asbestosis, have become less frequent due to declining exposure levels. The major determinant of pleural thickening is duration from first exposure (70).

It is unclear whether the relative frequency of diffuse and circumscribed pleural thickening has changed. The *International Classification of Radiographs of Pneumoconioses* (38) provides a basis for recording and classifying both types of pleural thickening, allowing correlation with indices of exposure and measurements of lung function. Manifestations of disease of the lung and of the pleura have become less evident and less characteristic on plain films as exposures have decreased. However, CT scan (including high-resolution images) detects pleural thickening not evident on the plain film, and sometimes fails to confirm apparent pleural thickening read on the plain film. Schemes to quantify extent of pleural thickening on CT scan have been published (55, 85). Rarely, interlobar pleural thickening may mimic lung nodules on CT scan (86).

Pleuritis: acute pleural effusion, chronic pleuritic pain. Asbestos may cause an acute pleural effusion, often lasting several months, that is exudative and often hemorrhagic, with variable numbers of erythrocytes, neutrophils, lymphocytes, mesothelial cells, and often eosinophils (87–89). It may occur early (within 10 years, unlike other asbestos-related diseases) or late after the onset of asbestos exposure (90). It may be superimposed on long-standing pleural plaques (91). Although it is usually asymptomatic, the acute pleural effusion due to asbestos may also be exuberant, with fever and severe pleuritic pain. It is sometimes detected only incidentally on a radiograph taken for another purpose (87, 88). The effusion may persist for months, present bilaterally, or recur on the same or the opposite side (87). A friction rub may be present (92, 93). The traces of pleural effusion may be observed years later as a blunted costophrenic angle or as diffuse pleural thickening. Acute pleuritis is thought to underlie many cases of diffuse pleural thickening. Of 20 insulators with a past history of definite pleural effusion, diffuse pleural thickening was detected on radiograph in 16 (90). Dose–response relationships or characteristic features of exposure associated with effusion have not been described.

Chronic severe pleuritic pain is rare in patients with asbestos-related pleural disease (92, 93). Vague discomfort appears to be more frequent. Studies examining the frequency of atypical chest pain in asbestos-exposed patients have not been performed. In the few cases described, it was present for many years, disabling, and often bilateral. Radiographic evidence of pleural disease ranged from plaques to extensive diffuse and circumscribed pleural thickening; several cases followed pleural effusions. The diagnosis of acute asbestos-related pleural effusion is by exclusion of other causes of acute pleuritis, and most often is not arrived at until the pleural space is fully explored and biopsied, generally by thoracoscopy. Differentiation from Dressler's syndrome is difficult in asbestos-exposed patients who have undergone recent cardiac surgery. Differentiation from mesothelioma or pleural extension of a pulmonary malignancy is critical, and may be difficult on clinical grounds (including positive gallium and positron emission scan). Pleural fluid cytology is useful for distinguishing benign from malignant effusions. It is not unusual for nonspecific effusions to precede mesothelioma by several years. If a malignancy has not manifested itself within 3 years, the effusion is generally considered benign.

The diagnosis of chronic pleuritis manifested by pleuritic pain is reached by excluding malignancies, because most other causes of acute pleuritis do not result in chronic pain. Malignancy is unlikely when pain persists for years with little or no clinical or radiographic change.

Plaques: circumscribed pleural thickening. Pleural plaques are indicators of exposure to asbestos. They are clearly the most common manifestation of the inhalation, retention, and biologic effect of asbestos. Their prevalence is most directly related to duration from first exposure; they are rare within less than 20 years. Pleural plaques consistent with asbestos exposure appear in chest films of 2.3% of U.S. males, a percentage that has been